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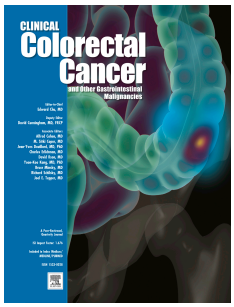

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Intestinal and extra-intestinal cancers associated with inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD) with its two most common entities, ulcerative colitis and Crohn's disease, causes an increased risk of developing intestinal cancers. In fact, malignancies are the second most common cause of death after cardiovascular diseases in both genders of patients with IBD. Risk factors for colorectal cancer in IBD correlate with the duration of the disease, extent of disease, the association with primary sclerosing cholangitis, family history, and early age at onset. Patients with IBD also have an increased risk for developing a variety of extra-intestinal malignancies. In particular, lymphomas, mostly non-Hodgkin lymphomas and skin cancers, are more frequently observed in IBD patients. Longstanding inflammation and the degree of immunosuppression as a result of IBD treatment appear to be the main driving factors for IBD-related carcinogenesis. This review provides an update on the clinical and pathological features of IBD-related intestinal and extra-intestinal malignancies.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Dysplasia; Colorectal cancer; Cholangiocarcinoma; Lymphoma.

INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a life-long immune-mediated chronic inflammatory disorder of the gastrointestinal tract. Both types of IBD are characterized by chronic inflammation with episodes of remission and relapses [1,2]. It is estimated that at least 0.4% of Europeans and North Americans live with inflammatory bowel disease [2]. IBD patients are associated with excess deaths from infection, cardiovascular diseases and cancers [3]. Malignancies are the second most common cause of death after cardiovascular diseases in both men and women with IBD [4].

IBD patients are at increased risk of developing carcinoma of the gastrointestinal tract, including colorectal carcinoma and small bowel adenocarcinoma. Both CD and UC carry an increased risk with the greater risk associated with UC. More recently, patients with IBD have also been shown to be at increased risk of developing extra-intestinal malignancies, such as lymphomas and skin cancers. This article focuses on the clinical and pathological features of IBD-related intestinal and extra-intestinal malignancies.

GASTROINTESTINAL MALIGNANCIES ASSOCIATED WITH IBD

IBD-related colorectal cancer

Increased risk of intestinal cancers in IBD patients have been identified in studies of population-based registries, nationwide cohorts and referral-center cohorts [1,5-8].

A meta-analysis of 116 studies by Eaden et al showed that the prevalence of colorectal cancer in patients with UC is approximately 3.7% [9]. The development of cancer accounts for one third of deaths related to UC. The risk begins to rise significantly above that of the general population approximately 8-10 years after diagnosis. Meta-analyses showed that the risk is 2% at 10 years, 8% at 20 years, and 18% at 30 years after onset [8,10]. Patients with more extensive bowel disease are at greater risk; the incidence of colorectal cancer in UC patients with extensive colitis (pancolitis) is 19 times higher than the general population compared to 4 times higher if the disease is limited to left-side colon only. The risk for colorectal cancer in patients with CD appears lower than patients with UC. However, Crohn's patients have a higher risk of developing small bowel adenocarcinoma compared to the general population [8, 11].

Due to a high prevalence of primary sclerosing cholangitis in IBD patients (particularly in UC patients), hepatobiliary cancers, especially cholangiocarcinoma, have been linked to IBD [12,13]. In such cases, those who have primary sclerosing cholangitis are at an even greater risk for colorectal cancer, and that increased risk is readily present at the onset of disease [14].

On average, patients with IBD who are diagnosed with colorectal cancer are younger than non IBD-related colorectal cancer patients. A family history of colorectal cancer is associated with a 2 to 3-fold risk of colorectal cancer in the general population. This risk is also seen in patients with UC. Like non-IBD patients, the overall survival for IBD -related colorectal cancers is driven primarily by age, co-morbidities, and cancer stage at diagnosis [14].

Pathogenesis of IBD-related colorectal cancers

Although similarities exist in the pathogenesis of IBD-associated and sporadic colorectal cancers, there are also many differences. Sporadic colorectal cancers develop via the classic adenoma-dysplasia-carcinoma sequence, in which loss of adenomatous polyposis coli (APC) gene function is considered the crucial first step that sets the stage for other molecular alterations, with TP53 mutations driving the later stages of carcinogenesis [8,15]. IBD-associated colorectal carcinogenesis also follows a multistep process from inflamed, regenerative epithelium, to hyperplastic epithelium, to flat dysplasia, and finally invasive adenocarcinoma. However, loss of APC function is much less frequent and usually occurs late in the colitis-associated dysplasia-carcinoma sequence [8,15]. Instead, mutation of p53 and chromosomal instability are relatively early events in IBD-associated cancer [8,15].

It is thought that the inflammatory process in IBD leads to oxidative stress-induced DNA damage of the affected mucosa [16,17]. Methylation of CpG islands in several genes seems to precede dysplasia, and is more widespread throughout the mucosa of patients with UC, hence this molecular change may represent one of the important genetic alterations in IBD-associated colon cancer [18]. Constant attempts at regeneration of the damaged gastrointestinal mucosa at areas of inflammation provide more opportunities for transcription

errors and the subsequent development of neoplasia via activation of procarcinogenic genes and inhibition of tumor suppressor genes [18-22].

Alteration in the colonic flora has also been proposed as a mechanism for increased cancer risk. Altered flora may increase the degree of inflammation, or possibly produce procarcinogenic substances [21,22]. *Bacteroides fragilis* and *Enterococcus feacalis* have been implicated as procarcinogens [21-23]. Disruption of intestinal homeostasis and aberrant immune responses to commensal bacteria lead to IBD. Recent data data suggest a critical role of the interaction between the commensal gut bacteria and the immune system orchestrated by CTLA-4, at the origin of ipilimumab-induced enterocolitis [24]. This is one of the most severe immune-related adverse events observed with anti-CTLA-4 immunotherapy. Accordingly, ipilimumab provokes diffuse inflammation of the gastrointestinal tract, causing diarrhea, high rate of colonic ulcerations, extensive colitis, and steroid failure. These presentations strikingly mirror naturally occurring inflammatory bowel disease. However, unlike what is seen in conventional IBD, endoscopic biopsies from ipilimumab-induced enterocolitis showed acute, not chronic inflammation [24]. Notably, immunotherapy has reached center stage in treatment of advanced cancers including melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma, bladder cancer and gastrointestinal carcinomas. Ipilimumab-induced IBD-like enterocolitis may become a challenging problem for oncologists and gastroenterologists.

The use of immunosuppressant to treat inflammatory bowel disease plays a role as well. Medical therapies that diminish the intestinal mucosal inflammatory response represent the foundation of treatment in IBD. However, prolonged immunosuppression may also increase the risk of cancer and allow neoplasia to advance at a faster rate [23,25]. In transplant

recipients, the use of thiopurines is associated with a high rate of cancer recurrence, particularly within the first two years following transplantation [26]. In patients with IBD, limited data suggest that no dramatic incidence of cancer recurrence is associated with the use of thiopurines or anti-TNF agents. However, there is a rationale for a two-year drug holiday from immunosuppressants after the diagnosis [27]. In addition to concerns about the development of de novo cancer in an IBD patient without a history of cancer, clinicians caring for patients with IBD are increasingly challenged with questions about IBD management after the development of cancer. Conversely, oncologists are often concerned about how to manage IBD in cancer patients. To make a most relevant, personalized treatment decision, gastroenterologists and oncologists need to work closely on a case by case basis and be aware of the potential impact of immunosuppressive drugs on cancers as well as of the epidemiology of the risk of developing a second malignancy in cancer survivors.

Colitis-associated dysplasia and dysplasia-associated lesion/mass (DALM)

Both sporadic and colitis-associated colorectal cancer arise from dysplastic precancerous lesions, but the morphology and timing of many of the proposed factors are distinct enough to classify the colitis-associated colorectal carcinoma as a unique entity [15,18,23,25].

Histologically, dysplasia is separated into 4 distinct categories: negative for dysplasia, indefinite for dysplasia (**Figure 1**), low grade dysplasia (LGD) and high grade dysplasia (HGD) (**Figure 2**). Among pathologists, there appears to be a high level of agreement on both negative for dysplasia and HGD, while the diagnoses of LGD or indefinite for dysplasia often have less agreement rate [15,28,29].

From an endoscopic (gross) point of view, colitis-related dysplasia may be classified as flat or elevated (raised) [30,31]. Flat dysplasia refers to endoscopically undetectable lesions, whereas raised dysplasia refers to plaque or polypoid mucosal appearance. Raised dysplastic lesion with an appearance of sporadic adenoma has been termed dysplasia-associated lesion or mass (DALM) [15,29,30] (**Figure 3**). Practically, the colitis-associated dysplasia often occurs in ill-defined flat mucosa, being detected on taking random biopsies rather than by identification of these lesions via endoscopic imaging [30,31].

Owing to extensive inflammation, epithelial regeneration and dysplasia may be difficult to distinguish endoscopically and histologically (**Figure 4).** In many instances, biopsies and endoscopic mucosal resections of polypoid mucosal lesions turned out to be inflammatory pseudopolyps without dysplasia. Moreover, a patient with IBD can develop a sporadic adenoma with HGD, as can any other patient. The pathological differential diagnosis between DALM and sporadic adenoma is difficult [15,29,30]. The lesions should be differentiated by combined analysis of histological growth pattern and gross appearance. In general, a dysplastic lesion without proper delineation to the surrounding mucosa that occurs in long standing IBD most likely represents DALM. Colitis-related dysplasia tends to be multifocal and is associated with a high cancer risk, up to 43-58%.

If the lesion can be completely resected, and surrounding mucosal biopsies are normal without evidence of dysplasia, the lesion may be considered more likely to be sporadic and managed in a fashion similar to that of non-IBD patients. Therefore, whenever an actual mass or polyp is identified and removed from IBD patient, biopsies of normal-appearing mucosa around the lesion should be obtained [28-32].

Colitis-related dysplasia may occur in any part of the colon, can be unifocal or multifocal, and cancer is often detected in the same area as the dysplasia [15,29,30]. Mucosal-mapping studies indicate that the chronically inflamed colonic mucosa of patients with inflammatory bowel disease undergoes a “field change” of cancer-associated molecular alterations before there is any histological evidence of dysplasia [33]. This suggests that the chronically inflamed colonic mucosa is primed to develop multifocal precancerous and cancerous changes. IBD-related colorectal cancer has a higher rate of synchronous and metachronous tumors [32,33]. Therefore, patients with DALM are recommended to undergo prophylactic proctocolectomy with ileoanal pouch. In contrast, the sporadic adenomas in IBD patients that are similar to those observed in non-IBD patients and which are treated by standard polypectomy [30,31].

Surveillance and prevention of colitis-related colorectal cancers

As IBD-related colorectal cancer in most instances develops from dysplasia, it serves as the best marker of cancer risk in patients with IBD [34,35]. Although it is readily detectable for an advanced tumor endoscopically (**Figure 5**), the precancerous and early cancer lesions are often flat and hard to be identified from an inflamed and distorted background. Diagnosis of colitis-associated dysplasia and early cancer is one of the big challenges in gastrointestinal endoscopy [34,35].

Multiple societies including the American Gastroenterology Association [36], the American College of Gastroenterology (ACG) [37], the American Society for Gastrointestinal Endoscopy (ASGE) [38], the SCENIC group [39], European group [40] and the British Gastroenterology Society (BSG) [41] have published recommended surveillance guidelines,

although they are all quite similar. These recommendations are based on disease duration and extent of disease. Colonoscopy screening should start 8 to 10 years after diagnosis, with colonoscopies performed every 1 to 2 years with pancolitis and after 15 years in patients with left-sided disease only, because the incidence of colorectal cancer increases after 8 years of disease. Biopsies should be taken in 4 quadrants every 10 cm, typically resulting in more than 30 biopsy specimens for histological assessment.

Newer endoscopic techniques, especially high-definition white-light colonoscopy and chromoendoscopy with mucosal dye-spraying, allows for the identification of abnormal-appearing mucosa and has been demonstrated to detect neoplasia at double the rate of standard white-light colonoscopy [39]. Therefore, some authorities have recommended using chromoendoscopy rather than standard white light colonoscopy to perform targeted rather than random biopsies [35,39]. For example, in a study by Rutter and colleagues [42], 100 patients with long-standing UC underwent 2 colonoscopic examinations back-to-back, i.e., a conventional colonoscopy followed by a second colonoscopic examination with chromoendoscopy using dye-spraying, with the goal of increasing the detection rate of subtle lesions. The authors found a total of 114 additional abnormalities detected in 55 patients using chromoendoscopy compared to conventional colonoscopy. Of these 114 abnormalities, 7 were dysplastic lesions. The authors concluded that a targeted biopsy examination with chromoendoscopy required fewer biopsies but, more importantly, detected 9 dysplastic lesions, 7 of which were visible only after chromoendoscopy. Moreover, this study suggested that a careful examination by chromoendoscopy with targeted biopsies may be more of an effective surveillance strategy than obtaining multiple random, non-targeted biopsies. Although more longitudinal studies are needed to compare the outcome of surveillance techniques, in the coming years, we anticipate that the newer endoscopic techniques move us

closer to a surveillance model that is targeted, has high sensitivity and specificity, and allows for real-time diagnosis and intervention [43].

Regular dysplasia surveillance colonoscopy remains the key element to decrease the risk of IBD-related colorectal cancers. The anatomic extent of disease and duration of IBD have long been held to be risk factors for colorectal cancer in chronic colitis, and recently some special risk groups have been identified which may require either more intensive surveillance or alternative approaches to cancer prevention. These include patients with primary sclerosing cholangitis, age at onset of disease, disease activity and patients with first-degree relatives with sporadic colon cancer. There is an emerging interest in potential chemopreventative strategies in both sporadic and colitis-associated colorectal cancer [44]. There also have been suggestive data that chronic maintenance 5-aminosalicylate use might reduce the risk of developing colorectal cancer. Recent data have suggested some potential preventative benefit of using ursodeoxycholic acid in patients with ulcerative colitis and primary sclerosing cholangitis [44].

Crohn's disease and small-bowel adenocarcinoma

Because CD also affects the small intestine, it is associated with increased rates of small bowel adenocarcinoma. Fortunately, this more aggressive cancer is not common in the general population, but patients with CD have a 20- to 30-fold risk of development of small bowel cancer. IBD-related small bowel cancer typically arises in the ileal lesions of patients with CD more than 8 years after diagnosis. Prolonged duration of stricturing disease has been associated with the development of small-bowel cancer in patients with CD [45-47]. It is often associated with previous or synchronous ileal dysplasia, which suggests that it may

complicate chronic ileal inflammation in CD through a dysplasia-carcinoma sequence similar to that seen in colorectal carcinoma [48].

IBD-related intestinal lymphoma

The risk of primary intestinal lymphomas is significantly higher in patients with IBD, but the absolute risk is low (0.1 per 1000 patient-years) [49]. The IBD-related intestinal lymphomas are mainly B-cell non-Hodgkin's lymphomas, typically arising in chronically inflamed intestinal lesions of middle-aged men with CD after 8 years of disease [49]. Epstein-Barr virus (EBV) is frequently identified in lymphoma cells, which suggests that local inflammation and use of immunosuppressant may play a role in these cases by promoting EBV infection and replication [50].

IBD and anal cancers

Anal cancers may arise in the fistulae of patients with long-standing (>10 years) fistulating perianal CD, with an incidence rate of approximately 0.2 per 1000 patient-years [51]. These cancers include adenocarcinoma and squamous cell carcinoma. Diagnosis is often delayed because of a nonspecific clinical presentation and because access to lesions is obscured by the presence of stenosis. Although immunosuppression after organ transplantation promotes human papillomavirus (HPV)-related anal carcinoma, the risk in patients with IBD who are receiving immunosuppressant treatment is unknown.

Primary sclerosing cholangitis and cholangiocarcinoma in IBD patients

Primary sclerosing cholangitis (PSC), a progressive cholestatic disease, is strongly associated with UC and to a lesser extent CD. Approximately 70%-80% of patients with PSC have concomitant IBD and about 1.4%-7.5% of patients with IBD will develop PSC [12-14]. PSC is characterized by progressive inflammation of the intrahepatic and extrahepatic bile ducts followed by fibrosis and in worst cases biliary cirrhosis with portal hypertension and liver failure (**Figure 6**). The most concerning complication of sclerosing cholangitis is the development of cholangiocarcinoma.

Cholangiocarcinoma occurs at a younger age in IBD patients than in the general population without IBD (56 years vs. 71 years, respectively). In Western countries, cholangiocarcinoma occurring in patients younger than 40 years old is almost always associated with IBD [12-14]. Notably, patients with PSC are also at increased risk of developing colorectal carcinoma. The overall survival rate of IBD-related cholangiocarcinoma is low because many patients present with unresectable or metastatic disease. Even in patients undergoing aggressive surgery, five-year survival rates are around 10-40%.

Cholangiocarcinoma is a form of adenocarcinoma arising from the epithelium lining the biliary ducts (**Figure 6**). It can occur in the small bile ducts within the liver, the big branches in the center of the liver (hilum) or in the main or common bile duct outside the liver. Similar to the development of IBD-related colorectal carcinoma, PSC-associated cholangiocarcinoma appears to follow a dysplasia-carcinoma sequence [12,14]. The molecular mechanisms of carcinogenesis in PSC are not well elucidated yet. The evolution from PSC to cholangiocarcinoma may result from DNA damage by biliary inflammation and bile acids in IBD patients with altered DNA repair functions [52,53].

Diagnosis of cholangiocarcinoma in PSC often requires a combination of imaging studies performed when clinical deterioration, such as worsening of jaundice, weight loss and abdominal pain, suddenly develops [54]. Magnetic resonance imaging (MRI) coupled with magnetic resonance cholangiography is generally considered the first-line investigation for the malignant transformation, while ultrasound examination seems to have better accuracy in discriminating cholangiocarcinoma from underlying PSC. Liver functional test, complemented by serological CA19-9 assessment at annual intervals may be recommended. Currently, there is no effective medical therapy that alters PSC disease progression. This may be partially explained by both the rarity of the disease, which makes it difficult to enroll enough patients for study designs of sufficient power, and the poor knowledge of the pathogenesis of the disease. Several agents have been proposed for the treatment of PSC. The best-known agent ursodeoxycholic acid that improves hepatobiliary secretion, has immunomodulatory properties, and has been associated with biochemical and histological improvements in PSC patients [54].

EXTRA-INTESTINAL MALIGNANCIES ASSOCIATED WITH IBD

Early and sustained healing of intestinal inflammation has become the ultimate objective of treatment in IBD. Immunosuppressant therapies, including thiopurines, anti-tumor necrosis factor, cyclosporine and methotrexate are frequently necessary for IBD management. Immunosuppressant may be carcinogenic by directly altering cellular DNA, impairing immune control of chronic infection by mutagenic viruses, or reducing immunosurveillance of tumor cells [55-57]. After adjusting for confounders, use of thiopurines in IBD has been shown to be associated with an overall relative risk of cancer of 1.3 to 1.7 in adequately powered cohort studies [55,56]. This excess risk is reversible after thiopurine withdrawal. Overall, cancers caused by immunosuppressive drugs represent a minority of the incident cancers observed in patients with IBD.

IBD and hematological malignancies

IBD patients show a trend towards higher risks of developing hematological malignancies. Compared with the general population, UC patients are significantly more likely to develop leukemia, with a standardized incidence rate of 2.0 (95% CI: 1.31 - 3.06) [57,58]. In CD patients, there is an increased risk for lymphoma, especially non-Hodgkin lymphoma, with a standardized incidence rate of 1.42 (95% CI 1.16 - 1.73) [58].

Thiopurines were shown to increase the incidence of non-Hodgkin's lymphoma after kidney transplantation [59]. Similar observations have been reported in patients with IBD [60,61]. Most of the thiopurine-promoted lymphomas are post-transplant-like EBV-associated B-cell lymphomas [50]. In these patients, non-Hodgkin's lymphoma is attributed to the cytotoxic

effects of thiopurines on EBV-specific immune cells that prevent the proliferation of EBV-infected B lymphocytes. Therefore, EBV infection may have an intermediate role between immunosuppressive treatment and lymphoma [50].

Patients with IBD exposed to thiopurines are also at increased risk of hepato-splenic T-cell lymphoma and post-mononucleosis lymphoproliferative disorder [60-62].

Skin cancers

Patients with IBD receiving immunosuppressive treatment are at increased risk of skin cancers [63]. The risk of non-melanoma skin cancer is notably increased in patients receiving thiopurines; the incidence rate ratio is 1.64 (95% CI: 1.51-1.78) [63-65]. Squamous carcinoma and basal cell carcinoma are the most common non-melanoma skin cancers diagnosed in IBD patients.

In contrast, the risk of melanoma in patients with IBD who were exposed to TNF-α antagonists has been reported to be 1.5 to 2 times higher than that in patients who were not exposed, which represents an incidence rate of 0.5 per 1000 patient-years [60,66].

The carcinogenic action of thiopurines could include an increased toxicity of ultraviolet A radiation on epithelial skin cells and a direct mutagenic effect on the gene encoding PTCH [60]. Given the excess risks of skin cancers associated with both IBD and the drugs used to treat it, specialists recommend all patients with IBD should practice sun protection and skin cancer surveillance from the time of diagnosis.

Cervical intraepithelial neoplasia and cervical cancer

It is known that immunosuppression results in a higher incidence of cervical intraepithelial neoplasia (CIN) compared with healthy control females [67,68]. The incidence of abnormal Papanicolaou smear in IBD women is 42.5% vs. 7% in controls ($P < 0.001$). In addition, women with IBD are more likely to have higher-grade lesions than controls ($P < 0.001$) [67].

There is a strong correlation between HPV and cancer of the cervix and anogenital regions. Immunosuppressant therapies for IBD patients decrease the activity and competence of the immune system and may increase the risk to HPV infection. It is currently recommended that all women with IBD, particularly those receiving immunosuppressant, strictly adhere to a screening program of cervical surveillance and undergo vaccination against HPV, when appropriate.

Urinary tract cancers

Transplant recipients receiving immunosuppressive regimens that include thiopurines are at increased risk for kidney and bladder cancer [59]. As compared with patients with IBD who had never taken thiopurines, patients who were currently using azathioprine were reported in a Danish registry study to have a higher incidence of urinary-tract cancers, whereas former users of azathioprine did not [56].

SUMMARY

Patients with IBD, including ulcerative colitis and Crohn's disease, are at increased risk of developing intestinal and extra-intestinal cancers. IBD-related malignancies are the second most common cause of death in both genders of UC and CD patients. The risk for development of intestinal carcinomas in patients with UC and CD appears to depend on the duration of disease, the severity of disease, family history of colorectal cancer, and the presence of PSC. The colorectal cancer risk begins to rise significantly above that of the general population 8-10 years after diagnosis. Therefore, patients with IBD should be monitored via an intensive surveillance program. This surveillance program should include colonoscopies every 1 to 2 years with multiple biopsies taken from the affected intestine. Diagnosis of colitis-associated dysplasia and cancer is one of the big challenges in gastrointestinal endoscopy, which might be improved by new endoscopic imaging techniques such as high-definition white-light colonoscopy and chromoendoscopy with mucosal dye-spraying. **Table 1** summarizes the clinicopathological features of IBD-related colorectal cancers and surveillance recommendations in comparison with sporadic and hereditary carcinomas [69-73].

Patients with IBD have also been shown to be at increased risk of developing extra-intestinal malignancies, such as lymphomas and skin cancers. Clinicians who at the front line in the management of IBD patients must keep in mind that IBD may be associated with extra-intestinal malignancies, especially in patients who have longstanding immunosuppressive therapies. Guidelines and recommendations including educating patients in self check and preventative measurements like sun protection should be developed and applied in clinical practice to minimize the risk of IBD-related extra-intestinal malignancies.

Prolonged chronic inflammation is assumed to underlie the cause of colitis-associated gastrointestinal carcinomas, with oxidative stress-induced DNA damage resulting in the activation of procarcinogenic genes and silencing of tumor-suppressor pathways. Further studies on colitis-associated dysplasia and carcinoma can help to elucidate the important role of the immune system and microbiota in the development of these malignancies. The degree of immunosuppression generated from anti-inflammatory treatment appears to be the main driving factors for IBD-related extra-intestinal malignancies.

Table 1. Clinicopathological features and surveillance recommendations of sporadic, IBD-related and hereditary colorectal carcinomas (CRCs)

	Sporadic CRCs	IBD-related CRCs	Hereditary CRCs
Clinicopathological features	• Sporadic CRC accounts for 70 percent of all colorectal cancer cases. It is caused by an accumulation of sporadic gene mutations acquired throughout life. Because it takes long time for a series of genetic mutations to accumulate, sporadic colorectal cancer tends to occur at a later age, typically after the age of 50. • Adenoma–carcinoma sequence is a well-established tumor progression model as a result of genetic mutations or other chemical modifications, causing inactivation or promotion of specific genes known as tumor suppressor and tumor promoter genes. • A stepwise progressive transformation can be seen in an adenoma with low grade dysplasia to high grade dysplasia and early invasive carcinoma (malignant polyp). • Commonly left sided, with a recent trend of right shift as age progresses	• Inflammatory bowel disease (IBD) related malignancies are the second most common cause of death in both genders of IBD patients. • Both sporadic and colitis-associated colorectal cancer arise from dysplastic precancerous lesions, but the morphology and timing of many of the proposed factors are distinct enough to classify the colitis-associated dysplasia/mass and IBD-related cancers as unique entities. • IBD-related colorectal cancer has a higher rate of synchronous and metachronous tumors. • Colitis-associated dysplasia/mass and IBD-related cancer may occur in any part of the colon. The lesions can be unifocal or multifocal, and cancer is often detected in the same area as the dysplasia.	• Recognized hereditary syndromes, such as familial adenomatous polyposis (FAP) and Lynch syndrome [69,70], account for up to 5% of cases of colorectal cancer. They are associated with germline mutations of genes, which predisposes the patient to a high risk of CRCs. Patients with these syndromes have a family history of colorectal cancer, presenting at an early age. • Lynch syndrome is the most common hereditary colon cancer syndrome. It accounts for 3-5% of all colorectal cancer cases. CRCs in Lynch syndrome tend to be mucinous, right sided colonic location and poor differentiation with signet ring cells. Another striking pathological feature is a high density of tumor-infiltrating lymphocytes. Despite poor histological differentiation, the biological behavior of these CRCs is less aggressive. • FAP accounts for 1 percent of all CRC cases. Patients with FAP develop hundreds to thousands of adenomas, usually starting in the teens. These polyps can be seen in any part of the colon and rectum.
Molecular genetics	• Dysplasia-carcinoma sequence involving chromosomal instability, microsatellite	• Inflammation-dysplasia-carcinoma sequence involving chromosomal instability,	• Lynch syndrome is an autosomal dominant disorder, caused by a

	instability and hypermethylation. • Most sporadic colorectal cancers arise from an adenomatous precursor lesion that progresses through various stages until it becomes carcinoma. Loss of APC gene function is considered the crucial first step that sets the stage for other molecular alterations, with p53 mutations driving the later stages of carcinogenesis. • Mutations in genes such as KRAS, NRAS, BRAF and MMR have linked to the pathogenesis of CRCs, and these molecular markers have become increasingly important in prediction of response to chemotherapy and immunotherapy.	microsatellite instability and hypermethylation. • Like sporadic CRCs, IBD-related CRCs are a consequence of sequential episodes of biological and molecular alterations, including immune response by mucosal inflammatory mediators, oxidative stress, and intestinal microbiota, leading to inflammatory damage, regeneration, dysplasia and carcinoma. • Precancerous/dysplastic lesion arises in the colitic mucosa and progresses through various grades of dysplasia. • Although many of the molecular alterations seen in sporadic CRCs occur in colitis-associated cancer, the timing and sequence of events often differs. For example, mutations in p53 gene or a loss of p53 function are seen early, whereas the loss of APC gene function is a late and less common event.	germline mutation in one of the mismatch repair (MMR) genes: MLH1, MSH2, MSH6 and PMS2 [69]. • Mutations in these genes results in defective DNA mismatch repair, leading to microsatellite instability, hypermutation and increased risk of developing malignant neoplasms. • Recent studies suggest that CRCs with a defect MMR are sensitive to checkpoint blockage drugs and microsatellite instability-high phenotype is a predictive biomarker for checkpoint immunotherapy [71]. • FAP is caused by mutation of adenomatous polyposis coli (APC) gene [70]. Most people inherit the genetic abnormality from a parent. But in about 25% of cases, the genetic mutation occurs spontaneously.
Cancer risks	• Cancer risk increase with aging and unhealthy lifestyle. • In addition, risk increase with previous detection of colorectal adenomas and number of adenomas.	• Risk factors for IBD-related CRCs correlate with the duration of the disease, extent of disease, the association with primary sclerosing cholangitis, family history, and early age at onset. • Meta-analysis shows that the cancer risk is 2% at 10 years, 8% at 20 years, and 18% at 30 years after IBD onset. Cancer risk begins to be significant 8 years after the onset of pancolitis (involvement of entire large intestine), or 12-15 years after the onset of left-sided colitis. • Incidence of colorectal cancer in patients with active pancolitis is 19 times higher than the general population. • IBD is also associated with increased risk of extra-intestinal cancers.	• Lynch syndrome is associated with 80% of risk of developing colorectal carcinoma. It also shows an increased risk of endometrial carcinoma (33%), ovarian carcinoma (5%), and cancers of small bowel, stomach, upper urinary tract, and brain. • Eventually, all FAP patients will develop colorectal cancer from the adenomas usually by age 40. Therefore, patients with FAP must have the colon, and sometimes the rectum, removed to prevent CRCs. FAP is also associated with increased risk of extra-intestinal cancers.

Surveillance recommendations	• In England, the NHS offers two types of bowel cancer screening to adults registered with a GP [72]: 1) All men and women aged 60-74 are invited to carry out a fecal occult blood test and every two years, they are sent a home test kit, which is used to collect a stool sample. 2) An additional one-off test called bowel scope screening is gradually being introduced in England. This is offered to men and women at the age of 55. Moreover, an appropriate colonoscopic surveillance strategy should be offered to people with adenomas based on their risk of developing colorectal cancer as determined at initial adenoma removal. • American Cancer Society [73] recommends men and women, starting at age 50, at average risk for developing colorectal cancer should regularly use fecal occult blood test, colonoscopy or double-contrast barium enema to detect polyps or cancers. People at increased or high risk will need to start colorectal cancer screening before age 50 and/or be screened more often.	• American Gastroenterological Association (AGA) [36] and European Crohn's and Colitis Organization (ECCO) [40] recommend that initial surveillance colonoscopy begin after 8 years of colitis or from the time of diagnosis of primary sclerosing cholangitis, at which time random biopsies or targeted colorectal biopsies should be performed. • British Society of Gastroenterology (BSG) [41] recommends beginning surveillance colonoscopy after 10 years of colitis, with chromoendoscopy as the preferred method. • For the ECCO and BSG, subsequent surveillance intervals are determined by stratifying patients into low-risk, intermediate-risk, and high-risk groups based on clinicopathological features. The overall clinical management depends on the histological findings and whether lesions are endoscopically resectable. • Guidelines and recommendations including educating patients in self check and preventative measurements like sun protection should be developed and applied in clinical practice to minimize the risk of IBD-related extra-intestinal malignancies.	• Family members with Lynch syndrome should have surveillance colonoscopy every 1 to 2 years, starting from 20-25 years, or 10 years before the youngest case in the immediate family. • Family members with FAP are recommended to have yearly colonoscopy to look for signs of adenomas, starting from age 10 to 12 until the patient and physician determine that a colectomy is the best treatment. • Upper endoscopic surveillance is also recommended for patients with FAP and Lynch syndrome.

Abbreviations: AGA: American Gastroenterological Association; APC: adenomatous polyposis coli; BSC: British Society of Gastroenterology; CRCs: colorectal carcinomas; ECCO: European Crohn's and Colitis Organization; FAP: familial adenomatous polyposis; IBD: inflammatory bowel disease; MMR: mismatch repair.

Legend of the figures

Figure 1

Top panel shows ulcerative colitis with crypt abscess formation, crypt distortion and active inflammation but negative for dysplasia. Bottom panel shows features of quiescent colitis with focal crypt epithelial atypia, indefinite for low grade dysplasia.

Figure 2

Comparison of low grade dysplasia (left panel) and high grade dysplasia (right panel). Note the high nuclear to cytoplasmic ratio, nuclear hyperchromasia and loss of nuclear polarity in high grade dysplasia.

Figure 3

Histology of an endoscopic mucosal resection specimen showing dysplasia-associated lesion/mass (DALM). The large bowel mucosa is thickened and composed of dysplastic glands showing mixed low and high grade dysplasia. Background chronic inflammation is present.

Figure 4

Colectomy specimen from a patient with ulcerative colitis showing the junction of diseased and non-diseased large bowel. Due to marked inflammation and mucosal distortion, it is hard to identify the dysplastic or early cancer lesions. This explains why the diagnosis of colitis-associated dysplasia and early cancer is difficult.

Figure 5

An advanced neoplastic lesion with central ulceration seen endoscopically (top panel). Biopsies show invasive adenocarcinoma (bottom panel).

Figure 6

Top panel shows primary sclerosing cholangitis (PSC). An intrahepatic bile duct is destroyed by chronic inflammation with surrounding laminated fibrosis. Bottom panel shows a cholangiocarcinoma arising on a background of PSC.

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